REMARKS

This Submission is responsive to the Office Action mailed October 1, 2009.

In claim 1, all occurrences of the variable Y in the formula $C_mH_{2m+o-p}Y_p$ have been changed to Y' such that the formula is now $C_mH_{2m+o-p}Y'_p$. Also, in claim1, the variable Y in the definition of heterocycloalkyl has been changed to Y''. These amendments were made to distinguish the variables from the variable Y that appears in Formula Ia and Formula Ib. No new matter has been added.

The specification has been amended, as discussed below, to amend the names of the variables in the synthetic schemes and Tables to be consistent with the names of the substituents in the claims and the remainder of the specification. The variable Y has also been amended in the same manner as claim 1. No new matter has been added.

REJECTION UNDER 35 USC 112, 1st PARAGRAPH, WRITTEN DESCRIPTION

At page 2 of the Office Action, the Examiner maintained the rejection of claims 1-7, 9, 15 and 16 as failing to comply with the written description rejection. The Examiner alleged that the claims still contain some groups that are not defined, such as "heteroaryloyl." The Examiner also noted that the specification and claims disclose two different R2 and R3, as well as different R1 and R5, so that these discrepancies do not give a clear and concise written description.

Applicants traverse this rejection.

"Heteroaryloyl" is clearly defined in the claims. Heteroaryloyl refers to the group (heteroaryl)–C(=O)–. Heteroaryl, by itself or as part of another substituent, is separately defined in claim 1.

The synthetic schemes and Tables in specification have been amended to change the names of variables to be consistent with Formula Ia and Ib, and the remainder of the specification and claims, and avoid duplication. On page 18, in Diagram 4 and Table 2, R has been changed to R'. On pages 19, in Diagram 5, R1 has been changed to R3, and R2 has been changed to R2'. On page 20, in Table 3, R1 has been changed to R2', and R2 has been changed to R3. On page 51, in Diagram 10 and Table 4, R1 has been changed to R2, R2 has been

changed to R3, and R3 has been changed to R5. On page 53, in Diagram 11 and Table 5, R1 has been changed to R3, R2 has been changed to R5, and R3 has been changed to R8.

The specification provides clear and concise written description of the claimed compounds and the manner of making and using them. Withdrawal of this section 112, first paragraph rejection is respectfully requested.

REJECTION UNDER 35 USC 112, 1st PARAGRAPH, ENABLEMENT

At page 5 of the Office Action, the Examiner maintained the rejection of claims 1-7, 9, 15 and 16 under 35 USC 112, first paragraph as not enabled. In the present Office Action, the Examiner alleged that because the definitions of R1, R2, R3 and R5 are not clear, and none of the examples given in the specification correspond to the derivatives as claims, it is not clear how the compounds are made. The Examiner also stated that there is an issue with availability of the starting material. The Examiner further alleged that it would require undue experimentation to use the claimed compounds for treatment of tumors.

Applicants again traverse this rejection.

The grounds for this rejection are based in part on discrepancies between the names of variables in the formulae recited in the claims and the synthetic schemes and Tables in the specification. The variables in the formulae in the diagrams and Tables have been amended to be consistent with the substituents in the claims, as discussed above. In view of the amendments to the specification, there can be no doubt that the specification enables persons skilled in the art to make the claimed compounds.

The Examiner also alleged that the starting materials for the claimed compounds is an issue, specifically whether the starting materials necessary to make the invention are available. Applicants submit that the starting materials for preparing the claimed compounds are readily available to persons skilled in the art. The claimed fredericamycin derivatives are prepared semi-synthetically starting with fredericamycin (see page 15 of the specification). Fredericamycin is well-known in the art and readily available. Fredericamycin A can be prepared by fermentation or fully synthetically according to known methods. As disclosed at page 1 of the specification, fredericamycin was isolated in 1981 from *Streptomyces griseus* and various total syntheses of fredericamycin have been described.

The Examiner also alleged that it would require undue experimentation to use the claimed compounds for treatment of tumors. The Examiner contended that the data in the specification is insufficient because Applicants have provided only averaged data from the cell lines for each compound tested, rather than presenting the data for each cell line separately. The Examiner contends that it does not make sense to average out the data for different activity and, therefore, to extrapolate the averaged data to treat tumors is an exaggeration.

Applicants' remarks in the response filed July 6, 2009 are incorporated herein by reference. Applicants continue to direct the Examiner's attention to MPEP 2107.03 "Special Considerations for Asserted Therapeutic or Pharmacological Utilities." Applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use as a matter of statistical certainty, nor does the applicant have to provide actual evidence of success in treating humans where such utility is asserted. Instead, all that is required is a reasonable correlation between the activity and the asserted use. Courts have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility as being supportive of an assertion of therapeutic utility for a new compound. If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.

The specification at page 57, lines 1-4 in the section entitled "Biological activity against 12 cancer lines" and Table 7 presents data on the antitumor activity of the claimed compounds. The specification shows the averaged results of the efficacy of over twenty compounds of the invention in *in vitro* assays with twelve cancer cell lines, representing lung, breast, melanoma, renal, uterine, and prostate tumors. Adriamycin, cisplatin and fredericamycin, three known antitumor agents were also tested and the results shown in Table 7. In Table 7 the compounds of the invention are shown by a number in the left column that correlates with the example of the same number in the Example section beginning at page 58 of the specification. The claimed compounds showed efficacy in the assays comparable to fredericamycin, and often the IC70 was lower than the IC70 of fredericamycin. The claimed compounds show the same efficacy as known antitumor agents in tests performed in the same manner. Thus, persons skilled in the art

would find the Applicants have provided sufficient to evidence establish therapeutic or pharmacological utility for the claimed compounds.

For at least the reasons discussed above, the data presented in the specification is believed to be sufficient to enable to persons skilled in the art to make and use the claimed invention throughout its scope for treatment of the types of tumors recited in claim 15 and parasites. The specification thus enables claims 1-7, 9, 15 and 16. Withdrawal of this section 112, first paragraph rejection is again respectfully requested.

REJECTION UNDER 35 USC 103

At page 8 of the Office Action, the Examiner rejected claims 1-7, 9, 15 and 16 under 35 USC 103 as being *prima facie* obvious over U.S. patents 4,584,377 (Yokoi et al.); 4,673,678 (Misra) and 5,166,208 (Kelly et al.). Duan et al., Delgado et al. and Okimoto et al. were also used to reject the claims. In the present Office Action, the Examiner maintained the rejection because of the broad definition of the variable groups. The Examiner alleged that the claims still have numerous generic definitions, and that glucose, fructose, other hetero groups, and cyclodextrin can all be encompassed by them.

Applicants again traverse this rejection. Claim 1 was previously amended to delete reference to sugars in substituents R5, R21 and R22.

A *prima facie* case of obviousness requires the following: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP at 2143.

The three cited patents, Yokoi et al., Misra and Kelly et al. each disclose fredericamycin A derivatives, but do not disclose or suggest the compounds of claims 1-7. Duan et al., Delgado et al. and Okimoto et al. disclose cyclodextrin for use in inclusion complexes with drugs that are poorly water soluble. There is no disclosure or suggestion, however, that the cyclodextrin complexes can be used with fredericamycin A derivatives.

Even if, for the sake of argument, the teachings of the references were properly combined, the combined teaching of the cited references would still not disclose the compounds

of claims 1-8, the drugs of claims 9-10 that contain the compounds of claim 1, or the methods of claims 15 and 16 which use the compounds of claim 1. At most, the combined teachings of the cited references would provide cyclodextrin inclusion complexes containing different fredericamycin derivatives than the claimed compounds.

The combined teachings of the cited references do not disclose or suggest all of the limitations of the compounds of claims 1-7. The fredericamycin derivatives of claims 1-7, drugs of claim 9, and the methods of claims 15 and 16 are therefore not *prima facie* obvious in view of the combined teachings of Yokoi et al., Misra, and Kelly et al., Duan et al., Delgado et al. and Okimoto et al. The present rejection is therefore improper and should be withdrawn . Withdrawal of this section 103 rejection is again respectfully requested.

In view of the above, the present application is believed to be in a condition ready for allowance. Reconsideration of the application is respectfully requested and an early Notice of Allowance is earnestly solicited.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 03-2775, under Order No. 14528-00001-US.

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Respectfully submitted,

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